To the

German Patent and Trademark Office

Munich

Dachau, October 1st 2003

Re: Utility model 201 16 428 Lö I 13/03
utility model N° DE 201 16 428 UI
Pharmaceutical compositions comprising
amlodipine maleate
Cancellation proceedings
Cancellation petitioner
CIMEX Development AG
Hauptstraße 67
CH-4102 Binningen/Basel
Switzerland

Cancellation Opponent
Pfizer Limited
261 Ramsgate Road
Sandwich, Kent CT13 9NJ, Great Britain
(formerly: BioOrganics BV
Toerniiveld 134
Nijmegen, Netherlands)

My ref.: GL 7 922

Re the Ruling of 17th July 2003 and the opposition reasoning by the Opponent, Pfizer Limited, 261 Ramsgate Road, Sandwich, Kent CT13 9NJ, Great Britain, dated 15th July 2003.

It is true we believe that the previous submission by the Petitioner proves the absence of protectability for the disputed utility model, however the statements by the Opponent cannot remain unopposed, whereby the following, for reasons of economy, will merely concentrate on the essential points.

1. The object of Protection Claim I, according to the main motion is, in relation to the document WIO 95/34299 (Annex ASt 2) not new, even based on the statements by the Opponent (opposition reasoning dated 15th July 2003, Section 1.2 Page 4, third last para.). The Opponent is arguing, in diametrical contrast to established German jurisprudence.

    a) The specification WO 95/34299 (Annex ASt 2) specifically cites amlodipine maleate(Page 6,

Lines 26 to 32 in connection with Page 7 Lines 27 to 32) and a pH value of ca. 6.5 to ca. 8.0 (Page 9 Line 25). As already stated in the cancellation petition, the range of ca. 6.5 to 7.0 falls within the range of 5.5 to 7.0 cited in Protection Claim 1 for the disputed utility model.

b) The fact that this disclosure is at various places in the citation does not indicate lack of novelty. To this end, as

Annex ASt 6

neutralised copies of the Ruling by the Federal Patent Court dated 13th June 1995 on Case 3 Ni 19/94 are being submitted as evidence:
From this Page 6, paras. 3 and 4 are quoted:

"Diethanol amine and tri-hydroxy methyl – aminomethane, which is identical to the 2-amino-2-hydroxy methyl-1,3-propandiol and hereinafter referred to as "TRIS" for short are each one of the total of 14 amine-containing hydroxyl groups that are named in the citation in connection with the statement that they can equally be used as water-soluble amines in the compositions under discussion (see Sp 4 Z 37 to 45).

As a consequence, the specialist can see from US-PS 3 681 492 not only the composition cited by way of example in Column 5 Lines 5 to 14, the composition containing ca. 0.5% diethanol amine but also those compositions containing TRIS instead of diethanol amine whilst retaining the given content.

Reference is also made to the Ruling BGH GRUR 1995, 330 "Electrical plug connection" cited in the above Ruling, in particular Line 332, left Column, Line 12 from below to right Column, para. 2.

The object of Protection Claim 1 of the utility model as defined in the main petition is, in other words not new in the light of Specification WO 95/34299 (Annex ASt 2). The transition to solid compositions (Protection Claim 1 as per alternative claims 1 and 2) is clear, solid substances do not have a pH, rather this only occurs in a watery medium, so that, to measure the pH, this solid preparations first has to be put into watery media.

2. The replacement, cited in US Patent Specification 6 057 344 (Annex ASt 5), Example 8, of amlodipine by the equivalent amount of amlodipine maleate as per Column 10 Lines 57 to 61 in connection with Column 10 Line 65 to Column 11 Line 4, was measured by the Petitioner through measurements in a 20% suspension of demineralised water having the pH value of 6.48 as shown in the following Table (Column A).

	A (g)	B (g)	C (g)
Amlodipine maleate	0.64	3,20	6.40
Lactose monohydrate	182.86	180.30	177.10
Gelatinised starch	15.0	15.0	15.0
Magnesium stearate	1.5	1.5	1.5
Total	200	200	200
pH	6.48	6.09	5.82

This Table also included pH values for other percentages of amlodipine maleate (Columns B and C) which also showed pH values within the pH ranges of 5.5 to 7.0, specifically 6.09 and 5.82) cited Protection Claim 1 for the disputed utility model.

Test A (repetition of Example 8 in US Patent Specification 6 057 344 (Annex ASt 5), in other words, in addition to the cancellation petition dated 27th January 2003, Page 7, para. 3 to Page 8 para. 3 in particular demonstrates the non-novelty of the object of Protection Claim 1 as per the main petition and alternative claims 1 and 2 compared to the US Patent Specification 6 057 344 (Annex ASt 5), whereby your attention is drawn to the jurisprudence cited under 1), in particular the Ruling by the Federal Patent Court in Case 3 Ni 19/54 as per Annex ASt 6. This too, as in this case, primarily relates to the exchange of one substance in one example for another from a list of substances in one and the same prior publication and thus the substantiation of non-novelty. Correspondingly in this case too there is a clear absence of novelty compared to the US Patent Specification 6 057 344 (Annex ASt 5).

3. It is correct that a saturated watery solution of amlodipine maleate has a pH value of ca. 4.8 (opposition reasoning dated 15th July 2003, Page 4 Lines 1 to 3). Dicalcium phosphate has a maximum pH value of 7.4, often below 7.0 (disputed utility model Specification, Page 8 para. 1). In other words minimum amounts of amlodipine maleate are sufficient to place the pH value in Protection Claim 1 for the disputed utility model within the pH range of 5.5 to 7.0, in

other words the compositions of amlodipine maleate and calcium hydrogen phosphate are, in practically volume ratios not alkaline. The, by way of experiment, the utility model Petitioner measured the following pH values in a 20% weight/vol suspension of amlodipine maleate and calcium hydrogen phosphate (=dicalcium phosphate) [$CaHPO_4$] {Fluka}.

Amlodipine maleate	$CaHPO_4$	Volume ratio	pH value
0.1 g	9.9 g	1/99	6.57-6.58
1 g	9 g	10/90	5.66+ – 5.67
0 g	10 g	0/100	7.23

The pH value of the used calcium hydrogen phosphate (dicalcium phosphate) amounted, as can be seen from the above Table, to 7.23. The volume ratio of amlodipine maleate: calcium hydrogen phosphate = 1:9 is close to the ratio of 12.8:126 = 1:10.2 in Example 1 (Page 13),

Section a) batch number (B) for the disputed utility model Specification (otherwise the ratio there of amlodipine maleate: calcium hydrogen phosphate is clearly always 1:10.2). In the normal quantitative compositions for amlodipine maleate preparations, in other words, the pH values are within the range petitioned in Protection Claim 1 for the disputed utility model. Thus US Patent Specification 5 155 120 (Annex ASt 1) also predates the objects of objects of Protection Claim 1 and alternative claims 1 and 2, in relation to this prior publication, they are also, in addition to the reasons discussed in the cancellation petition on Pages 4 to 6, para. 2, not new.

Although, with the above clear facts of the case, especially as the fact of the absence of patentability of the object for the disputed utility model was justified by absence of novelty, the salient aspect is not whether, from current technological perspectives, the effect of the claimed acid pH range could not be derived as countering the breakdown of the maleate from amlodipine maleate, your attention is also drawn to the following for the sake of completeness.

4a) In this connection your attention is first drawn to the American Journal of Health System Pharmacy, Vol. 55, June 1st 1998, Pages I 155 to I 157, a copy of which appended as

Annex ASt 7

in particular Table 1 on Page I 156, right Column, bottom

and

Page I 155, right Column, last Line to Page I 156, left Column, Line 2.

"Boulton et al found enalapril 0.1 and 1 mg/ml (as the maleate) to be stable for at least 30 days at 5°C in a solution of isotonic citrate buffer solution (pH 5.)"

This shows that enalapril maleate was stable with a pH value of 5.1. It is true this pH value of

5.1 is slightly below the pH cited in the disputed utility model with its lower limit of 5.5, however this prior publication instructs the specialist, with maleate salts of active ingredients with amino groups, to set acidic value of 5.5 to attain good stability.

From this the specialist could also deduce to proceed similarly with amlodipine maleate since it is clear on the basis for the disputed utility model Specification, in particular Page 4, Line 1 after the formula to the last Line after the formula that the Michael addition reaction of the active ingredient (there amlodipine) with the maleic acid and thus the salt formation of the maleic acid with the active ingredient (there amlodipine) is responsible for an essential breakdown reaction of the amlodipine maleate. Enalapril, just like amlodipine forms a salt with maleic acid.

b) Moreover Specification WO 98/26765, of which a copy is appended as

Annex ASt 8,

in particular Page 1, Lines 11 to 15

"As it is known, many compounds that inhibit ACE (Angiatensia-Converging Enzyme) have poor stability either in form of free acids or salts if they are in a pharmaceutical dosage form. These compounds easily decompose fast of all by hydrolysis and intramolecvlar eyclization, but the amount of other decomposition products not identified in many cases may be also signicant. This is particularly true in case of enalapril and its maleate salt',

Page 3, Lines 8 to 17

"The aim of our invention is to prepare pharmaceutical formulations of high stability which contain enalapril maleate with commonly used filling substances (e.g. lactose, mannitol, sorbitol) lubricant (e,g. magnesium stearate) and disintegrating agents (e.g. starch) and in which the amount of decomposition products is low even in case of long-term storage, thus ensuring a longer expiration time and in the same time a high quality.

It has been found that if ealapril maleate is transformed into pharmaceutical formulations by applying commonly used filling substance (eg- filling substance of saccharide type) and malcic acid stabilizer, an extemely stable enalapril formulation is obtained. This is true even if magnesium stearate or other compounds are used as lubricants, affecting the stability of enalapril maleate.'

and

Page 3, Lines 27 to 29

"One of the preferred variant farns of our invention is the tablet or the granules for filling capsule consisting of enalapril maleate, maleic acid, lactose. starch, partly hydrolysed starch and magnesium stearate, and optionally colouring and binding agents"

and the examples and the Protection Claims 1, 5, 6, 11, 12 and 14.

It is clear that enalapril maleate with the weak acid maleic acid has a pH value near to or within the petitioned disputed utility model pH range, since, with the slightly acid citrate buffer colution, a pH value slightly under the pH range attained in the disputed utility model would be attained.

It should be noted that it is true that in the Patent Specification WO 98/26765 (Annex ASt 8) the focus is on other decomposition reactions, however it is stated in the above initial quotation (Page 1 Lines 11 to

15, in particular Lines 13 to 14) that the volume can also be signficant for other decomposition products. This also includes the aspartate obtainedd by the Michael addition.

c) This Michael Addition of "methylene compounds", whiuch also include maleic acid was generally known before the priority date for the disputed utility model. In this context, your attention, for example, is drawn to RÖMPP CHEMIE LEXIKON, 9th ed, 1991, Page 2 771, left Column, key word Michael Addition, of which copies and the title Pages are appended as

Annex ASt 9.

5. Moreover we append an extract from the Journal of the American Pharmaceutical Association, vol. 39, n° 3, May/June 1999, Pages 375 to 377, of which copies are appended as Annex ASt 10

In particular Table 1 on Page 376 top and Page 376, right Column, third-last para, Lines 1 to 7

"In each extemporancousty prepared suspension, amlodipine besylan was stable for 91 days at 4°C and 56 days at 25°C (Table 1). No noticeablechanges in color or odour war observed in any sample, during the 91-day study period: the pH changed slightly in 1% methyl cellulose/syrup formulation at 25°C. This data should be useful for preparing a liquid dosage form of amlodipine for pediatric patients who are unable to swallow tablets".

(text appears to be missing) known stability of amlodipine besylate in suspensions with a pH value of 6.5/6.69, i.e. within the range defined in the disputed utility model of 5.5 to 7.0 was suitable to guide the specialist in the direction of utility model application of a pH range between 5.5 to 7.0. It is true that the amlodipine besylate maleate/maleic acid plays no role but it is important for the specialist, with another salt of the same active ingredient, to try with the same pH values, since the last-cited publication shows that the pH values of 6.5/6.69 do not have any detrimental decompostion effect on the amlodipine, but rather keep this stable.

The above, with refutation of the argumentaiton of the cancellation Opponent, further substantiates the non-novelty of the objects of Protection Claim 1 as in the main application and alternative claims 1 and 2.

We request that the Court take this submision into consideration when preparing a provisional Ruling.

Patent lawyer

Annexes:
Copies of this pleading
dated 1st October 2003 duplicate

Neutralised copies of the Ruling
of the Federal Patent Court dated
13th June 1995 in Case 3 Ni 19/94
(Annex ASt 6) triplicate

Copies of the American Journal of
Health System Pharmacy
Vol. 55, June 1st 1998
Page 1 155 to I 157
(Annex ASt 7) triplicate

Copies of the Patent Specification WO 98/26765
(Annex ASt 8) triplicate

Copies of RÖMPP CHEMIE LEXIKON
9th ed 1991
Page 2 771 and the title Pages
(Annex ASt 9) triplicate

Copies of the Journal of the American
Pharmaceutical Association, Vol. 39
№ 3, May/June 1999, Pages 375 to
377
(Annex ASt 10) triplicate

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1st October 2003
Utility model 201 16 428 Lö I 13/03
Utility model n° 201 16 428
GL 7922

Supplement to list of Annexes

Neutralised copies of the Ruling
of the Federal Patent Court dated
13th June 1995 in Case 3 Ni 19/94
(Annex ASt 6)

American Journal of
Health System Pharmacy
Vol. 55, June 1st 1998
Page 1 155 to I 157
(Annex ASt 7)

Patent Specification
WO 98/26765 (Annex ASt 8)

RÖMPP CHEMIE LEXIKON
9th ed 1991
Page 2 771
(Annex ASt 9)

Journal of the American
Pharmaceutical Association, Vol. 39
N 3, May/June 1999, Pages 375 to
377
(Annex ASt 10)

Ast 6

IN THE NAME OF THE PEOPLE

Pronounced on
13th June 1995
Strixner
Secretary and
Clerk to the Court

3 Ni 19/94
(Case n°)

In the patent revocation action

Plaintiff

Versus

Defendant

re patent DE 36 12 538

The 3rd Senate (Revocation Senate III) of the Federal Patent Court at the hearing on 13th June 1995 with the participation of the presiding judge Grüttemann and the judges Dr. Rupprecht, Dr. Holzner, Dr. Philipp und Judge Sredl

has approved the petition.

Patent 36 12 538 is thus partially revoked in that the Protection Claim contains the following wording:

"The sodium salt of 2-(ethyl mercurithio)-benzoic acid or phenyl mercury borate as preservative, to be administered as ophthalmic medicine in drop form free of ascorbic acid, distinguished by the fact that to stabilise the preservative medium, it contains 2-amino-2-(hydroxymethyl)-1,3 propandiol or homologue thereof with up to 10 C-atoms in a volume of 0.2 to 1% weight."

The other action is rejected.

The costs of the proceedings are offset against each of the parties.

Facts of the case

The Defendant is the registered holder of Patent 36 12 538, applied for on 14th April 1986 (disputed patent), which relates to the stabilisation of mercury-containing preservation media in eye drops and which comprises two patent claims. Protection Claim 1 reads:

"A mercury-containing preservation media to be administered as ophthalmic medicine in drop form free of ascorbic acid, distinguished by the fact that to stabilise the preservative medium, contains 2-amino-2-(hydroxymethyl)-1,3 propandiol or homologue with up to 10 C- atoms"

Protection Claim 2 relating to Protection Claim 2, your attention is drawn to the Patent Specification.

The Plaintiff is claiming that the object for the disputed patent cannot be patented since it is not new or based on invention as can be derived from US Patent Specification 3 681 492, US Patent Specification 4 524 063, US Patent Specification 1 862 896 and the British Patent Specification 1 173 661.

The Plaintiff is requesting the revocation for the disputed patent.

The Defendant, at a hearing, has submitted a new (single) Protection Claim and declared that it will only defend the disputed patent within the scope of this new application. This Protection Claim reads as follows:

"An ophthalmic medicine with a mercury-containing preservation medium to be administered in drop form distinguished by the fact that to stabilise the preservation medium, it contains 2-aminino-2-(hydroxymethyl)-l,3-propandiol or a homologue thereof with up to 10 C-atoms in a volume of 0.2 to 1% weight."

It petitions:

The rejection of the action where this is directed at the disputed patent within the sphere being defended.

Alternatively it moves that the disputed patent have added a version of the Alternative Claims 1 or 2. The wording of the Alternative Claim1 corresponds to the tenor of The Ruling.

The Defendant contests the Plaintiff's submission and deems the object for the disputed patent in the defended version to be patentable.

Reasons for decision:

The patent action is partially justified. This applies to the disputed patent in the no-longer defended version; to this extent it is to be revoked to lack of defence. The action is also correct with regard to the defended version for the disputed patent.

However the alleged reason for invalidity due to lack or patentability, §§ 22 para. 1, 21 para 1 Nr 1 in connection with § § 3, 4 Patent Act does not apply for the Protection Claim under Alternative Claim 1.

The defended version for the disputed patent is a composition of the awarded Protection Claims 1 and 2. The admissibility of this limited defence is beyond doubt. The new Protection Claim for the main action is thus to be used as the basis for the objective evaluation for the disputed patent.

1) The disputed patent relates to an ophthalmic medicine in drop form containing a mercury-containing preservation medium. Such preservation media have the disadvantage that over the course of time they form deposits on the internal surface of plastic containers and thus lose their preservative quality. Moreover mercury-based preservative media have only a low level of stability in aqueous solutions.

2) The disputed patent is alleged to provide an ophthalmic medicine with a mercury-based preservative that remains stable over a lengthy period of storage and use.

3) To this end the disputed patent, in its defended form, defines a preparation with the following features:

1- Ophthalmic medicine,
1.1 administered in drop form,

2. Containing a mercury-based preservative,

3. To stabilise which 2-Amino-2-(hydroxymethyl)1,3-propandiol, or

4. Or a homologue thereof,
4.1 Containing up to 10 C-atoms,

5 In a volume of 0.2 to 1% weight

The object of the defended Protection Claim (main action) is not new. Even after the insertion of the content details "in a volume of 0.2 to 1% weight", Protection Claim 1 also covers ophthalmic medicines that the specialist could derive from US Patent Specification 3 681 492.

From this perspective of the citation, bactericidal aqueous solutions are known which contain ascorbic acid or certain ascorbic acid derivatives, a copper salt dissociated in copper ions and a water-soluble amine capable of providing stability for copper complexes (see Protection Claim there).

Moreover this also shows the use of such solutions as ophthalmic medicines (see Column 2 Line 29 to 33 and Line 50 to 54) and a formulation serving as an example that, alongside ascorbic acid,

ammonium chloride, copper sulphate pentahydrate and distilled water, also contains merthiolate und diethanol amine (see Column 5 Line 5 to 14)

The name used here of "merthiolate" is merely another name for the identical mercury compound named, in the disputed patent as the sodium salt of 2-(ethylmercurithio)-benzoic acid ("thiomersal") which is one of the most common mercury-based preservative media.

Diethanol amine und Tris-hydroxymethyl-amino-methane, identical to the disputed patent's 2-amino-2-hydroxymethyl1,3-propandiol and abbreviated hereinafter to "TRIS", are both one of the total of 14 amines containing hydroxyl groups, that are cited by name in this citation in connection with the finding that can be used as water-soluble amines to the same extent in the compounds cited there (see Column 4 Line 37 to 45).

As a consequence the specialist can see from US Patent Specification 3 681 492 not only the compound, cited by way of example in Column 5 Line 5 to 14 containing ca. 0.5% diethanol amine but also those compounds that also contain TRIS, instead of diethanol amine whilst retaining the given content.

Since the claimed Protection Claim in the main action does not exclude the medicines applied for in the disputed patent (which in this specialist area are based on known active ingredients and the application of "ophthalmic medicine in drop form") which can also contain ascorbic acid and

copper ions in the form of copper sulphate pentahydrate, a specialist's consideration of TRIS as a water soluble amine in a pharmaceutical formulation as cited in Column 5 Line 5 to 1 can lead to an anticipation of the medicines as defined in the defended Protection Claim which speaks against claims of novelty.

This situation is not altered by the Defendant's restriction made through inclusion of specification of the content range of 2-amino-2-hydroxymethyl-l,3-propandiol, since the citation's example for the content of water-soluble amine (ca. 0.5 %) falls within this range.

As the Federal Supreme Court stated in the Ruling "Electrical Plug Connection" (GRUR 1995, 330), the specialist, here too in the opinion of the Parties a pharmacist with experience in the formulation of ophthalmic medicines (Ophthalmology), is to "use as a yardstick" what, under § 3 para. 1 sub-para. 2 Patent Act has been made "accessible to the public" (op cit p. 331). This Ruling also stated that, in the matter of by what criteria prior publications are to be subjected to novelty examination under § 3 para. 1 of the Patent Act, the most precise wording of the prior publication can

be precisely as non-determining as the fact of whether the disclosure of the prior-published technical data is derived from the Protection Claims or the description. The salient object of a protected right also includes such adaptations that, according to the overall context of the Specification, suggest themselves to the specialist, with careful reading, less of the words but more of the recognisable gist, such that he to a certain extent comes to think along certain lines, even if he is unaware of this. Under these preconditions something will also be to a large extent regarded as disclosed detrimental to novelty if it is circumscribed often in literature with the vague and, for delimitation, less suitable term of the well-known, specialist exchange medium (see op cit Line 332).

In this instance, the anticipation detrimental to novelty of the ophthalmic medicine being applied for in the Protection Claim is derived from US Patent Specification 3 681 492 on the basis of the specialist's exchange of diethanol amine (see Column 5 Line 5 to 14), for TRIS (see Column 4 Line 37 to 45).

III

1. The Protection Claim under Alternative Claim 1 (for the full wording, see the Ruling) differs from the defended Protection Claim in that the "mercury-containing) preservation medium is restricted to the sodium salt of 2-(ethyl-mercurithio)-benzoic acid or phenyl-mercury borate and the ophthalmic medicine is free of ascorbic acid. These restrictions are permissible since, they are covered through the publication in the original documents and the Patent Specification (see Examples 1 and 2) and do not expand the protected range of the patent. The novelty of the object of the Protection Claim under Alternative Claim 1 exists compared to the publication in US Patent Specification 36 81 492 since ascorbic acid-free ophthalmic medicines are not included in this citation; the specialist can see from the application and description that the compounds cited there have to contain ascorbic acid and copper ions (see too Column 1 Line 15 to 17 and Column 2 Line 1 to 5).

The object of the Protection Claim under Alternative Claim 1 is also new in relation to the eye solutions known from US Patent Specification 4 524 063. This printed matter does include ophthalmic medicines that can contain antimicrobial additions from various chemical compound classes, but only in context cites phenyl-mercury nitrate (Column 2 Line 59 to 60), the use of which is not included in the Protection Claim for the disputed patent under Alternative Claim 1.

2. The formulation of the ophthalmic medicine to be administered in drop form under Alternative Claim 1 can also not be approximately derived from the state of technology.

Thus the technical science of US-PS 3 681 492 is intended to extend the anti-microbial effect of the aqueous solution containing ascorbic acid and copper ions, which only lasts seconds or minutes (see Column 1 Line 41 to 45), through the addition of nitrogen compounds in a controllable manner to a period of days (see Column 5 and 6). Where the selection of these nitrogen compounds is made from the water soluble amines group, this must absolutely be based on the criterion that the common logarithm of the stability constants of complexes of copper ions and such amines, in the given pH range of 5 to 8 must lie between 3 and 14 (see Protection Claim). As stated below under II, for example, diethanol amine and TRIS under this criterion are equally suited to form copper complexes. However here the specialist gets no reference to the suitability of this or that amine cited in the US Patent Specification (see Column 4 Line 37 to 45) for the stabilisation of mercury-based preservatives, since the aim for the disputed patent is not to extend the antimicrobial effect of the ascorbic acid/copper ion system to a period of several days but rather to satisfy the requirement, known from "Pharmacy 1977", that for industrially-manufactured eye drops, the aim must be for a storage life of several years. This results in higher requirements for stability of the overall content, including the preservation medium (see op cit Page 99, left Column para. 3). The examples contained in the disputed patent also show that the disputed patent contains formulations that can be kept for 4 to 5 years at room temperature (see Page 3 Line 44- 45 und Page 4 Line 17 - 18)

In the light of the differing nature of the problems, the US Patent Specification does not give the specialist any reason to test whether any of the nitrogen compounds used there as complex-builders for copper ions could be suitable for solving the underlying problem of the long-term stabilisation of mercury-based eye drops.

Moreover the US Patent Specification 4 524 063 does not provide the specialist with any indications for solving the problem underlying the disputed patent. This document merely states that it was for the first time possible, through the addition of polyvinyl alcohol to an aqueous solution with the active ingredient as N, N.-(2-chlor-5-cyan-m-phenylen)dioxamate and 2 mol TRIS, to prepare a pharmaceutical compound through the use of which the topical effectiveness of this substance was reinforced for the treatment of allergic reactions with eyes (see Column 1 Line 29 to 46).

Due to the quite different and quite specific problems, the aforementioned citations thus give the specialist no indication of any solution of the problem underlying the disputed patent.

In the view of the Plaintiff, an examination of US Patent Specification 3 681 492 together with the oldest available documents, the 1932 Patent Specification 1 862 896, leads the specialist to the science for the disputed patent. The latter document is cited as an invention object for stabilising certain alkyl mercury sulphur compounds which without such stabilisation tend to form decomposition compounds (see p 1 Line 1 to 4). The mercury compounds to be stabilised are there generally designated as effective antiseptics and bactericides (see p 1 Line 19 to 23)

The US Patent Specification 1 862 896 by contrast contains no details for the application of the ophthalmic medicine in drop form. The allegation by the Plaintiff, that the object of US Patent Specification US-PS 1 862 896 is also geared to ophthalmic therapy is not attested by the content of the citation. The claim that the reference to mucous membranes on Page 1 Line 53 to 56 also includes the conjunctiva of the eye is not confirmed in distributed medical dictionaries under the key word "mucous membrane".

Individually then it is stated in US Patent Specification 1 662 896 that, where there are mercury compounds to be stabilised in aqueous solutions, it is necessary to keep the hydrogen ion concentration absolutely within the alkaline range, if possible between pH 8 and pH 10.5 since the mercury compounds are otherwise present as free carbonic acids and can form a deposit (see p 1 Line 40 to 48). Since the solutions under discussion, when kept, can cause irritation to the skin and mucous membranes, they are less suitable in unstabilised form for use as antiseptics or bactericides (Page 1 Line 56 to 66).

This US Patent Specification cites the addition of an anti-oxidant to the solution to be stabilised, naming for example, a water-soluble aliphatic amine, specifically citing monoethanol amine, triethanol amine or Di-n-butyl amine (see Page 1 Line 67 to 75). The preferred example cited for such a stabilised solution is in particular mixing an aqueous solution containing "merthiolate" with monoethanol amine and by adding borax obtaining a pH of ca. 8, or better between 9.5 and 10, maintaining this and finally essentially rendering this solution isotonic through the addition of sodium chloride (see Page 1 Line 81 to 91).

The specialist defined above must, in 1986, have regarded the expressly cited example of a watery solution of merthiolate as unusable for the preparation of ophthalmic medicine for application in drop form. The procedure specified there of obtaining a pH of ca. 8, and preferably obtaining and maintaining a pH of 9.5 to 10 is not followed in the latest technology in the area of eye drops.

Thus US Patent Specification 3 681 492 cites setting the pH for ophthalmic medicine to a value of 6.5 to 7.4 (see Column 2 Line 50 to 54).

The publication "Therapeutic Review" 17, 1973, 469 to 483, states that the specialist will in general try to keep the pH of an ophthalmic preparation as near to 7.0 as possible (see Page 473 left Column Line 13 to 16), whereby with regard to the stability of mercury-based preservative media it is additionally stated that the use of Thiomersal is strictly limited to alkaline or neutral solutions (see Page 475 left Column para. 3 Z 4 to 6).

In the documented submitted by the Plaintiff, K. Thoma, Ophthalmology, 2nd ed, Munich 1960, Page 12 to 13, it is true it states that pH values of isotonic buffer solutions between pH 7.3 and 9.7 were tolerated without irritation by the test subjects. However the reference to this test result is not to be considered as doctrine stipulating a pH value of up to 9.7 when formulating ophthalmic solutions. Rather it states on Page 13 para 1 that ready-made medicaments often have to offer a compromise between stability, tolerance and effectiveness.

Moreover the science cited in US Patent Specification 1 862 896 (see Page 1 2 81 to 91) of making an aqueous solution containing a merthiolate, monoethanol amine and Borax essentially isotonic by addition of sodium chloride, will not be followed by the specialist since he is aware from the current state of technology, (see "Pharmacy" 32, 1977, Page 99 to 100) of the special tests on the stability of thiomersal in eye drops and knows that it is clearly the constituent sodium chloride that, in an aqueous solution containing thiomersal, exercises the decisive influence on the chemical decomposition (see Page 100 left Column para 1). This publication confirms that the problem shown in the disputed patent was an objective one (see Page 99 left Column Summary and Introduction, also there last para. and right Column para 1 und right Column para. 1 last sub-para.)

The complexity of the requirements facing the specialist is summarised in "Therapeutic Review" 1973, where it states that specific requirements have to be considered for medical eye drops (see Page 471 left Column para. 1 last sub-para; S 472 right Column para 1; S 473 left Column para 1). In particular it makes it clear on Page 478 "Discussion', that one cannot use one set of results (active ingredient/preservative/auxiliary material) from one formulation to extrapolate to another, even if only minor changes have been made.

The evaluation, derived from the opinion of the specialist world, in "Therapeutic Review" 1973 and quite specifically the stability of Thiomersal in eye drops as per the tests in "Pharmacy" 1977, make it least appear doubtful whether the specialist, defined as a pharmacist with experience in formulating eye medicaments (ophthalmology) would even bother to consult the 1932 US Patent Specification 1 862 896

(the same also applies analogously to the British Patent Specification 1 173 661) when carrying out targeted research in relation to the disputed Patent Specification (see Page 2 Line 37 to 39).

Even if, as a result of broad research, this should be the case, it must be assumed that the pharmacist does not regard this document as being cutting-edge technology for the formulation of ophthalmic medicine and would put it to one side because the scientific doctrine propounded there and which states that the preparation of solutions as eye drops should lie within an unusual pH range, definitely alkaline and preferably between 8 and 10.5 (see Page 1 Line 40 to 46 and Line 87 to 90) would not provide any impetus to the resolution of his problem.

The Senate also regards these deliberations as confirmed in that US Patent Specification 1 862 896 (as also the British Patent Specification 1 173 661) are not cited in the relevant publications "Pharmacy" 1977 and "Therapeutic Review" 1973 and thus are not included with the preparation and therapeutic application of the ophthalmic specialist field.

In comparison with the aforementioned citations, the science in the British Patent Specification 1 173 661, which, without a reference to ophthalmic medicines (see Page 1 Line 25 to 31 and Line 68 to 71) and organic mercury addition compounds presents a more advanced state of technology that was also not taken up by the Plaintiff at the hearing before the Senate.

The cost ruling is based on § 84 para. 2 Patent Act in connection with § 92 para. 1 Code of Civil Procedure.

Grüttemann	Dr. Rupprecht	Judge Dr. Holzner Is on holiday and thus cannot sign Grüttemann	Dr. Philipp	Sredl

only 64 patients were matched and included in the analysis, approximately 200 patients were treated on the service over the two study months. Finally, only drug acquisition costs were analyzed. Patient outcomes and related health care costs were not included.

Conclusion

HIV-positive patients required more pharmacist interventions, used more medications, and had higher medication costs than HIV-negative patients. The interventions for HIV-positive patients produced greater cost savings. Although the intervention rate for HIV-positive patients was more than twice that for negative patients, high-impact interventions occurred at similar rates in both groups.

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Stability of enalapril maleate in three extemporaneously prepared oral liquids

MILAP C. NAHATA, RICHARD S. MOROSCO, AND THOMAS F. HIPPLE

Abstract: The stability of enalapril 1 mg/mL (as the maleate) in deionized water, citrate buffer solution, and a sweetened suspending agent at two temperatures was studied.

Twenty enalapril 10-mg tablets were crushed to a powder. Deionized water, citrate buffer solution, or sweetened vehicle was added to produce three 200-mL batches of each liquid; the expected final concentration of enalapril in each was 1 mg/mL. Each formulation was stored in 10 60-mL bottles, 5 of which were stored at 4 °C and 5 at 25 °C. Samples were collected on days 0, 7, 14, 28, 42, 56, 70, and 91 for visual inspection and analysis by high-performance liquid chromatography; pH was measured at each sampling time as well.

The mean concentration of enalapril in the three liquids at 4 °C was >94% of the initial concentration throughout the 91-day study period. At 25 °C, the mean concentration of enalapril was >90% for 56 days and >92% for 91 days in both citrate buffer solution and sweetened vehicle. The pH of the liquid prepared with deionized water and stored at 25 °C decreased by 2.0 pH units.

Enalapril 1 mg/mL (as the maleate) in three extemporaneously compounded oral liquids was stable for 91 days at 4 and 25 °C with the exception of enalapril in deionized water, which was stable for only 56 days at 25 °C.

Index terms: Buffers; Cardiac drugs; Citric acid; Compounding; Enalapril maleate; Incompatibilities; Stability; Storage; Suspending agents; Suspensions; Sweetening agents; Tablets; Temperature; Vehicles; Water

Am J Health-Syst Pharm. 1998; 55:1155-7

Enalapril maleate is frequently used in infants and young children for the treatment of hypertension and congestive heart failure. It is commercially available as 2.5-, 5-, 10-, and 20-mg tablets. The initial dosage is usually 0.1 mg/kg/day for infants and children.[1] No liquid dosage form is commercially available for pediatric patients. In addition, there are limited data on the stability of enalapril in extemporaneously prepared oral liquids.

Boulton et al.[2] found enalapril 0.1 and 1 mg/mL (as

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the maleate) to be stable for at least 30 days at 5 °C in a solution of isotonic citrate buffer solution (pH 5). However, there are no known stability data for enalapril in readily available vehicles such as carboxymethylcellulose in syrup. Our study was designed to determine the stability of enalapril maleate in deionized water, citrate buffer solution, and a sweetened suspending agent at 4 and 25 °C.

Methods

Twenty enalapril maleate 10-mg tablets[a] were used to prepare three 200-mL batches of each liquid. In each case the tablets were crushed to powder by using a mortar and pestle, and the powder was mixed with deionized water[b]; citric acid buffer, pH 5[c]; or a 1:1 mixture of Ora-Sweet[d] and Ora-Plus[e] (appendix). None of the liquids was filtered to remove insoluble excipients. The nominal final concentration of enalapril in each liquid was 1 mg/mL.

Each of the enalapril formulations was stored in 10 60-mL plastic prescription bottles.[f] Five bottles of each formulation were stored at 4 °C in a refrigerator,[g] and the other five bottles were stored at 25 (±1) °C in a temperature-controlled water bath.[h] After thorough shaking, a 0.5-mL sample was collected from each bottle on days 0, 7, 14, 28, 42, 56, 70, and 91, visually examined, and analyzed in duplicate by a high-performance liquid chromatographic (HPLC) method.[2] The pH was measured at each sampling time as well.

The HPLC instrumentation consisted of a pump, an autosampler, and a variable-wavelength ultraviolet-light detector[i]; an integrator[j]; and a C_8 column.[k] A digital pH meter,[l] a wrist-action shaker,[m] and a Vortex mixer[n] were also used. The mobile phase consisted of 65% 20 mM potassium phosphate monobasic[o] and 35% acetonitrile.[p] Before use, the mobile phase was passed through a 0.45-µm nylon 66 filter[q] and then degassed with helium. The flow rate was 1 mL/min. The detector was set at 215 nm, and the injection volume was 10 µL. The column was maintained at 80 °C. The chemicals and reagents, including phosphoric acid,[r] buffer solution pH 7,[s] buffer solution pH 4,[t] and buffer solution pH 10,[u] were American Chemical Society or analytical grade. Under these conditions, enalapril eluted at 2.9 minutes.

A stock solution of enalapril reference standard[v] was prepared in water and diluted to yield concentrations of 1.5, 1.25, 1, 0.75, 0.5, and 0.1 mg/mL. One hundred microliters of each of these solutions was then mixed with 900 µL of mobile phase and analyzed, as were the samples.

In order to establish the stability-indicating nature of the method, enalapril in water was forcibly degraded by acid[w] and base[x] hydrolysis and oxidation[y] at 60 °C. The sample was processed as described earlier. The peaks for the degradation products appeared at 1.2, 4.6, and 7.8 minutes and did not interfere with the quantitation of enalapril. Chromatograms of the oral liquids without enalapril were compared with chromatograms of enalapril standard; constituents of the oral liquids were found not to interfere with the measurement of enalapril. Linearity of the standard curve was determined by linear regression analysis of the enalapril concentrations (0.1–1.5 mg/mL) versus peak height of enalapril; the correlation coefficient was greater than 0.999. The accuracy of the method ranged from 99.2% to 101.6%, and the interday and intraday coefficients of variation were less than 4%.

Enalapril was considered stable if its concentration after storage was ≥90% of the initial concentration.

Results

At 4 °C, the mean concentration of enalapril in the three liquids was >94% of the initial concentration throughout the 91-day study period, but at 25 °C, the mean concentration was >90% for 56 days in deionized water and >92% for 91 days in both citrate buffer solution and the sweetened suspending agent (Table 1). The physical appearance of the liquids remained unchanged, and pH did not change by more than 0.1 pH unit except in the liquid prepared with deionized water and stored at 25 °C, in which case pH decreased by 2.0 pH units.

Table 1.
Stability of Enalapril 1 mg/mL at 4 and 25 °C

	% Initial Concentration Remaining[a]		
Day	Deionized Water	Citrate Buffer Solution pH 5.0	1:1 Mixture of Ora-Plus and Ora-Sweet[b]
At 4 °C			
0	100.0 ± 1.0[c]	100.0 ± 1.2[d]	100.0 ± 3.6[e]
7	98.6 ± 1.3	98.7 ± 1.6	99.4 ± 4.8
14	98.1 ± 1.4	99.1 ± 1.9	98.6 ± 5.3
28	97.6 ± 1.9	98.7 ± 2.0	98.4 ± 5.9
42	97.1 ± 1.9	98.5 ± 1.3	97.9 ± 4.2
56	96.5 ± 1.1	97.3 ± 1.2	96.9 ± 5.0
70	95.2 ± 1.3	96.3 ± 2.2	96.1 ± 5.3
91	94.8 ± 1.8	95.9 ± 1.3	95.8 ± 5.9
At 25 °C			
0	100.0 ± 1.0[f]	100.0 ± 1.2[g]	100.0 ± 3.3[h]
7	98.3 ± 1.4	98.2 ± 1.8	99.7 ± 5.2
14	96.4 ± 2.1	97.0 ± 1.9	98.1 ± 5.9
28	94.1 ± 3.3	95.8 ± 2.5	96.2 ± 6.3
42	92.4 ± 2.4	95.3 ± 1.8	96.2 ± 4.4
56	90.1 ± 3.5	94.9 ± 2.6	95.7 ± 5.2
70	87.6 ± 4.1	93.9 ± 2.4	94.4 ± 5.7
91	84.1 ± 4.7	92.7 ± 2.7	93.8 ± 6.1

[a] Mean ± S.D. of duplicate determinations for five samples.
[b] Paddock Laboratories.
[c] The actual mean ± S.D. initial concentration was 0.99 ± 0.05 mg/mL, and the initial pH was 7.1.
[d] The actual mean ± S.D. initial concentration was 0.99 ± 0.01 mg/mL, and the initial pH was 5.1.
[e] The actual mean ± S.D. initial concentration was 1.01 ± 0.04 mg/mL, and the initial pH was 4.7.
[f] The actual mean ± S.D. initial concentration was 0.97 ± 0.02 mg/mL, and the initial pH was 7.1.
[g] The actual mean ± S.D. initial concentration was 0.98 ± 0.03 mg/mL, and the initial pH was 5.1.
[h] The actual mean ± S.D. initial concentration was 0.99 ± 0.01 mg/mL, and the initial pH was 4.7.

Discussion

The formulation with deionized water would be the least expensive of the three formulations to prepare and its vehicle the most accessible. However, if a suspending agent with a sweetener is desired, enalapril can be prepared with equal volumes of commercially available Ora-Plus and Ora-Sweet.

Because of the lack of stability data, some doses of enalapril maleate have been dispensed as a powder prepared by diluting crushed tablets with lactose. This practice is cumbersome and labor-intensive, however. The knowledge that enalapril maleate is stable in widely available vehicles should simplify the preparation and delivery of weight-specific doses to infants and young children.

Conclusion

Enalapril 1 mg/mL (as the maleate) in three extemporaneously compounded oral liquids was stable for 91 days at 4 and 25 °C with the exception of enalapril 1 mg/mL in deionized water, which was stable for only 56 days at 25 °C.

[a]Merck & Co. Inc., West Point, PA, lot 02698.
[b]Deionized water type I, Children's Hospital, Columbus, OH.
[c]Children's Hospital, lot C139601MMCH.
[d]Paddock Laboratories, Minneapolis, MN, lot SK6734, containing purified water, sucrose, glycerin, sorbitol, flavoring, citric acid, sodium phosphate, methylparaben, and potassium sorbate, pH 4.2.
[e]Paddock Laboratories, lot 4E6462, containing purified water, microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, flavoring, citric acid, sodium phosphate, simethicone, methylparaben, and potassium sorbate, pH 4.2.
[f]Ol Owens-Illinois, Toledo, OH.
[g]White-Westinghouse, White Consolidated Inc., Columbus, OH.
[h]Lauda RM20, Brinkmann Instruments, Inc., Westbury, NY.
[i]HP 1050 series, Hewlett-Packard Co., Analytical Products Group, Palo Alto, CA.
[j]HP 3396A, Hewlett-Packard.
[k]Zorbax Reliance C_8 column, 5 µm, 4.0 × 160 mm, MAC-MOD Analytical, Chadds Ford, PA.
[l]Model 701A, Orion Research Inc., Boston, MA.
[m]Burrell Corp., Pittsburgh, PA.
[n]Vortex Genie 2, Fisher Scientific, Pittsburgh, PA.
[o]Sigma Chemical Co., St. Louis, MO, lot 16H1604.
[p]Burdick & Jackson, Division of Baxter, Muskegon, MI, lot BL893.
[q]Gelman Sciences, Ann Arbor, MI, lot 0082205.
[r]Mallinckrodt Inc., Science Products Division, St. Louis, MO, lot 2796 KESK.
[s]Fisher Scientific, lot 910090-24.
[t]Fisher Scientific, lot 910043-23.
[u]Fisher Scientific, lot 906524-24.
[v]United States Pharmacopeial Convention, Inc., Rockville, MD, lot H1.
[w]Hydrochloric acid, Mallinckrodt Specialty Chemical Co., Chesterfield, MO, lot AB12KBSV.
[x]Sodium hydroxide, Aldrich Chemical Co., Milwaukee, WI, lot 001LODY.
[y]Hydrogen peroxide, Aldrich Chemical, lot 05427TX.

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Appendix—Procedure for compounding enalapril maleate oral liquid

1. Count out 20 10-mg enalapril tablets.
2. Crush the tablets in a mortar.
3. Add a small volume of the vehicle,[z] and triturate to make a smooth paste.
4. Add increasing volumes of the vehicle to make the enalapril liquid pourable.
5. Transfer the liquid to a graduated cylinder.
6. Add enough vehicle to bring the final volume to 200 mL.
7. Label the bottle "Shake Well Before Using" and "Protect From Light."
8. Label with an expiration date: 91 days if prepared with citrate buffer solution or sweetened suspending agent; 91 days if prepared with deionized water for storage in the refrigerator; 56 days if prepared with deionized water for storage at room temperature.

[z]Use deionized water, citrate buffer solution, or a commercial sweetened suspending agent. Prepare the isotonic citrate buffer solution (pH 5.0) by dissolving 0.353 g of Citric Acid Monohydrate Granular, USP, 1.01 g of Sodium Citrate Dihydrate Granular, USP, and 0.54 g of sodium chloride in 100 mL of distilled water. Prepare the sweetened suspending agent by mixing equal volumes of Ora-Plus and Ora-Sweet (Paddock Laboratories).

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(57) Abstract

The invention relates to pharmaceutical compositions of enalapril maleate stabilized by maleic acid.

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Stabilized pharmaceutical compositions and pr cess for the preparation thereof

The present invention relates to novel stabilized pharmaceutical compositions, process for their preparation and the use of maleic acid as a stabilizer. The active ingredient of the above compositions is enalapril maleate which is a potent angiotensin-converting enzyme inhibitor, and it is useful in the treatment of hypertension.

Enalapril, its salts and the process for their preparation are described in the European Patent Application publ. No. EP-012401 A1.

As it is known, many compounds that inhibit ACE (Angiotensin-Converting Enzyme) have poor stability either in form of free acids or salts if they are in a pharmaceutical dosage form. These compounds easily decompose first of all by hydrolysis and intramolecular cyclization, but the amount of other decomposition products not identified in many cases may be also significant. This is particularly true in case of enalapril and its maleate salt.

Main decomposition products of enalapril are shown in Fig. demonstrating that the decomposition is due to hydrolytic and cyclization processes.

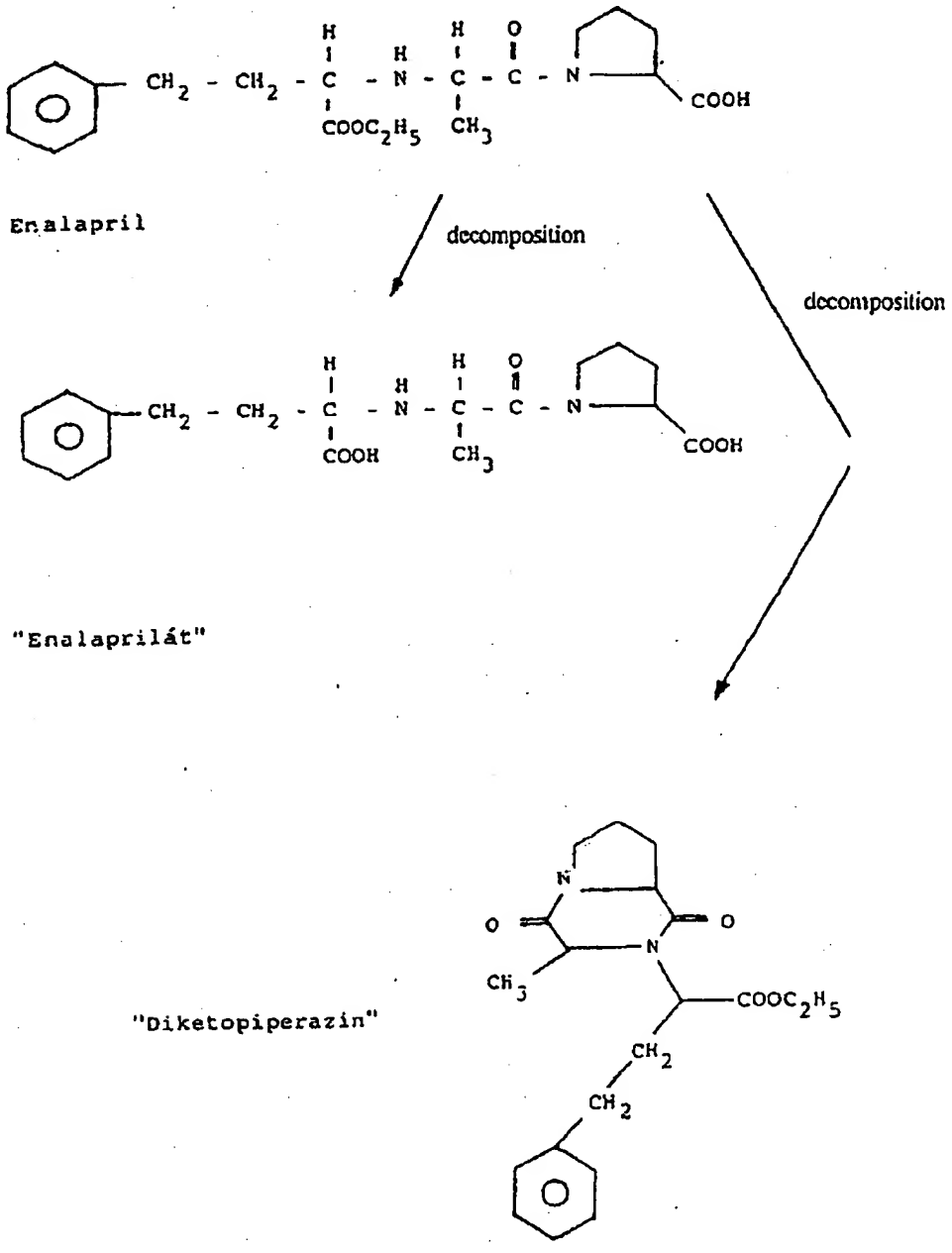
The diketopiperazine (DPK) is the internal cyclization product and the diacid (enalaprilat ET) is the product of ester hydrolysis.

A lot of solutions have been elaborated to stabilize angiotensin-converting enzyme inhibitors, among them enalapril salts in pharmaceutical compositions.

According to the European Patent Application publ. no. EP-0 280 999 A2, magnesium carbonate shows a stabilizing effect in pharmaceutical products containing saccharides, e.g. lactose and quinapril.

According to the European Patent Application publ. no. EP-0 545 194 A1, enalapril is transformed into its sodium salt. The enalapril sodium salt in pharmaceutical preparations is said to be more stable than the enalapril maleate salt.

Fig.


Enalapril
decomposition
decomposition
"Enalapriláť"
"Diketopiperazin"

United States Patent no. 5.562.921 describes that the enalapril maleate salt extensively decomposes in the presence of commonly used vehicles, filling substances, lubricants or disintegrating agents in many pharmaceutical products for example in the pharmaceutical dosage forms containing microcrystalline cellulose, calcium phosphate or magnesium stearate.

It is described in EP-A-099239 and EP-B-0264887 that ascorbic acid may be used as an antioxidant or colour stabilizing agent in case of ACE-inhibitors.

The aim of our invention is to prepare pharmaceutical formulations of high stability which contain enalapril maleate with commonly used filling substances (e.g. lactose, mannitol, sorbitol) lubricant (e.g. magnesium stearate) and disintegrating agents (e.g. starch) and in which the amount of decomposition products is low even in case of long-term storage, thus ensuring a longer expiration time and in the same time a high quality.

It has been found that if enalapril maleate is transformed into pharmaceutical formulations by applying commonly used filling substance (e.g. filling substance of saccharide type) and maleic acid stabilizer, an extremely stable enalapril formulation is obtained. This is true even if magnesium stearate or other compounds are used as lubricants, affecting the stability of enalapril maleate .

At realizing our invention, we have successfully applied for example mono- or disaccharides, water-free lactose, lactose monohydrate or DC (direct compression) lactose as filling substances, starches or partly hydrolysed starches, or crospovidone (polyvinylpolypyrrolidone) as disintegrating agents, magnesium stearate, hydrogenated vegetable oil or talc as lubricants, and maleic acid as stabilizer, in addition to the currently used colouring and binding agents, e.g. ferric oxide and povidone (polyvinylpyrrolidone). Further auxiliary substances applicable for these purposes are enumerated in the Hungarian Pharmacopoeia or in the European Pharmacopoeia.

One of the preferred variant forms of our invention is the tablet or the granules for filling capsule consisting of enalapril maleate, maleic acid, lactose, starch, partly hydrolysed starch and magnesium stearate, and optionally colouring and binding agents.

Our invention also relates to the process for the preparation of the above pharmaceutical formulations. During this process, granules to be compressed in tablets or to be filled into capsules are prepared by wet granulation using aqueous solution of maleic acid.

During one of the favourable implementations of the above process, dry enalapril maleate, lactose, starch and partly hydrolysed starch are mixed, and then their mixture is granulated using aqueous solution of maleic acid used as granulation liquid. Of course, ingredients may be mixed in other sequences. The granules obtained are dried and classified, and then compressed into tablets with magnesium stearate added.

Tablets according to our invention can be prepared by direct tabletting, i.e. mixing enalapril maleate with all other auxiliary substances and with maleic acid used as stabilizing agent, and by compressing the mixture in tablets.

Pharmaceutical products (dosage forms) prepared according to our invention may preferably contain enalapril maleate in 0.1-25 weight %, lactose in 30-95 weight %, starch and partly hydrolysed starch in 6-80 weight %, maleic acid in 0.1-10 weight %, lubricant in 0.1-5 weight % and colouring and binding agents in 0.01-5 weight %.

Preferred dosage forms are tablets and granules which contain enalapril maleate in 1.5-15 weight %, lactose in 65-90 weight %, starch and/or other disintegrating agents in 5-15 weight %, binding and colouring agents in 3-7 weight %, pregelatinized starch in 1-4 weight %, maleic acid in 1-5 weight % and lubricants in 0.1-1.5 weight %. Most preferred unit dosage forms are tablets with 75-300 mg tablet mass having above preferred compositions.

Further details of our invention are shown by the examples below, without limiting our claims to the examples.

Examples

Example 1

100 g of enalapril maleate, 3930 g of lactose monohydrate, 380 g of corn starch, 120 g of pregelatinized starch were homogenized. 24 g of maleic acid was dissolved in 1000 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 20 g of magnesium stearate (for 10-20 min).

The homogenized granules were tabletted and tablets having 115 mg total mass and containing 2.5 mg of enalapril maleate were obtained.

Example 2

150 g of enalapril maleate, 5934 g of lactose monohydrate, 570 g of corn starch, 180 g of pregelatinized starch were homogenized. 36 g of maleic acid was dissolved in 1500 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 30 g of magnesium stearate (for 10-20 min).

The homogenized granules were tabletted.

Example 3

200 g of enalapril maleate, 3300 g of lactose monohydrate, 300 g of corn starch, 100 g of pregelatinized starch were homogenized. 48 g of maleic acid was dissolved in 950 ml purified water. The homogenized powder mixture was granulated by slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate (for 10-20 min).

The homogenized granules were tabletted.

Example 4

250 g of enalapril maleate, 1890 g of lactose monohydrate, 188 g of corn starch, 68 g of pregelatinized starch were homogenized. 60 g of maleic acid was dissolved in 600 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 45 g of magnesium stearate (for 10-20 min).

The homogenized granules were tabletted and tablets having 200 mg total mass and containing 20 mg of enalapril maleate were obtained.

Example 5

200 g of enalapril maleate, 3300 g of lactose monohydrate, 300 g of corn starch, 100 g of pregelatinized starch, 48 g of maleic acid were homogenized. The homogeneous powder mixture was granulated with slowly (10-15 min) added purified water (950 ml). The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate (for 10-20 min).

The homogenized mixture was tabletted.

Example 6

3300 g of lactose monohydrate, 300 g of corn starch, 100 g of pregelatinized starch were homogenized. 48 g of maleic acid was dissolved in 1100 ml of purified water. While stirring, 200 g of enalapril maleate was added. The homogeneous powder mixture was added to the suspension. The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate.

The homogenized granules were tabletted.

Example 7

250 g of enalapril maleate, 4200 g of lactose monohydrate, 370 g of corn starch, 120 g of pregelatinized starch were homogenized. 45 g of maleic acid was dissolved in 1300 ml of purified water. While stirring, 120 g of polyvinylpyrrolidone was added to the pure solution. The

homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid and polyvinylpyrrolidone. The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate (for 10-20 min).
The homogenized granules were tabletted.

Example 8

250 g of enalapril maleate, 60 g of maleic acid, 45 g of magnesium stearate, 120 g of polyvinylpyrrolidone, 120 g of pregelatinized starch were homogenized. 370 g of corn starch, 4200 g of lactose monohydrate were added to the homogeneous mixture and the mixture was homogenized again (for 15-20 min).
The homogeneous mixture was tabletted.

Example 9

200 g of enalapril maleate, 1600 g of lactose monohydrate, 1600 g of corn starch, 250 g of pregelatinized starch, 100 g of polyvinylpyrrolidone, 150 g of talc were homogenized. 50 g of maleic acid was dissolved in 1000 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate.
The homogenized granules were tabletted.

Example 10

200 g of enalapril maleate, 250 g of pregelatinized starch were homogenized, 100 g of polyvinylpyrrolidone, 150 g of talc, 50 g of maleic acid and 40 g of magnesium stearate were homogenized. To the homogeneous mixture 1600 g of lactose and 1600 g of corn starch were added. The mixture was homogenized (for 15-20 min).
The homogenized mixture was tabletted.

Example 11

100 g of enalapril maleate, 1700 g of lactose monohydrate, 40 g of crospovidone, 110 g of maize starch and 2 g of ferrous oxide red were homogenized. 48 g of maleic acid was dissolved in 1200 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried at 40-50°C. The dried granules were homogenized with 10 g of magnesium stearate for 20 min.. The homogenized granules were tabletted and tablets having 200 mg total mass and containing 10 mg of enalapril maleate were obtained.

CLAIMS

1. Stable pharmaceutical composition, characterized in that, it contains enalapril maleate as active substance, maleic acid as stabilizing agent and one or more auxiliary substances.

2. Composition according to claim 1, characterized in that, it contains enalapril maleate in 1.5-15 weight %, filling substances in 65-90 weight %, disintegrating agents in 6-20 weight %, maleic acid in 1-5 weight %, binding and colouring agents in 3-7 weight % and lubricants in 0.1-1.5 weight %.

3. Composition according to claim 1, characterized in that, it contains mono- or disaccharides as filling substance, starches and/or crospovidone as disintegrating agent, stearate salts or esters, or hydrogenated vegetable oils as lubricants.

4. Composition according to claim 1, characterized in that, it contains enalapril maleate as active substance, maleic acid as stabilizing agent, lactose as filling substance, starch and crospovidone as disintegrating agent, magnesium stearate, hydrogenated vegetable oil or talc as lubricant, povidone as binding agent and optionally ferric oxide as colouring agent.

5. Composition according to claim 1, characterized in that, it contains enalapril maleate as active substance, maleic acid as stabilizing agent, lactose monohydrate as filling substance, starch as disintegrating agent, magnesium stearate as lubricant and optionally ferric oxide as colouring agent.

6. Composition according to claim 1, characterized in that, the dosage form is a tablet.

7. Composition according to claim 6, characterized in that, the dosage from is a tablet having 75-300 mg of tablet mass.

8. Composition according to claim 1, characterized in that, the dosage form is a capsule filled with granules.

9. Process for the preparation of composition according to claim 1, characterized in that, wet granulation is used.

10. Process according to claim 9, characterized in that, wet granulation is carried out with aqueous solution of maleic acid used as stabilizing agent.

11. Process according to claim 9, characterized in that, the enalapril maleate, lactose, disintegrating and colouring agents are mixed, dried, aqueous solution of stabilizing maleic acid is added, the mixture is wet granulated, the obtained granules are dried, classified, mixed with lubricant and compressed into tablets.

12. Use of maleic acid to stabilize enalapril maleate in a pharmaceutical composition as defined in anyone of claims 1 to 8.

13. Use of maleic acid as stabilizing agent in the manufacture of a pharmaceutical composition containing enalapril maleate as defined in anyone of claims 1 to 8.

14. Composition according to claim 1, characterized in that, it is in a commercial package in the form of orally applicable dosage form together with instructions for its administering.

01.10.03

INTERNATIONAL SEARCH REPORT

Ir. .ational Application No
PCT/HU 97/00084

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20 A61K31/40 A61K47/12

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classdication system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 793 998 A (MURTHY KUCHI S ET AL) 27 December 1988 see abstract see column 1, line 21-27 see column 2, line 15-18 see column 3, line 34-38 see column 4, line 24 see column 4, line 43-56 see column 5, line 18-20 see column 5, line 32-41 see column 5, line 54-61 see claims 5,7,8 --- -/--	1,6,8, 12-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 468 929 A (SANDOZ LTD) 29 January 1992 see page 2, line 11 see page 2, line 50-53 see page 4, line 7-8 see example 5C see page 7, line 56 - page 8, line 6	1,3,5-7, 9,10, 12-14

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Michael addition. Named after the American chemist, Arthur Michael (1853 – 1942), this reaction was first described in 1887. An activated methylene compound (cf Knoevenagel condensation) is added in the presence of a base to alkenes with electron acceptor radicals. It is therefore a nucleophile conjugate addition (1.4 addition) of a carbanion – produced from the methylene compound using the base – to an activated alkene. The methylene components used are malonester, cyanessigester, acetessigester and other compounds with activating radicals e.g. sulfonyl or nitro radicals. Indenes and fluorenes can also be metathesised successfully. Michael adducts are seldom obtained in the case of *a, β* unsaturated aldehydes as alkene components since here the addition to the carbonyl function (1.2 addition) is preferred. Silylene ethers [unclear] can also be used instead of activated methylene compounds.[1] it is also possible to carry out [illegible] and [illegible] Michael additions.[2]

[illegible diagrams]

As in the case of other reactions of carbonyl compounds, the resulting addition products can be further metathesised. The Michael addition often follows an intramolecular Aldol Addition (e.g. Robinson annealing).

[1]. Bull. Chem. Soc. Jpn, 48, 779 (1976)

[2]. Chem. Ber. 116, 3086 (1983)

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01-10-03 Ast 10

RESEARCH

Stability of Amlodipine Besylate in Two Liquid Dosage Forms

Milap C. Nahata, Richard S. Morosco, and Thomas F. Hipple

Objective: To determine the stability of amlodipine besylate in two liquid dosage forms under refrigeration and at room temperature. ***Design:*** Commercially available amlodipine tablets (Norvasc—Pfizer) were used to prepare two suspensions: one in extemporaneously prepared 1% methylcellulose in syrup (1:1), and another in equal volumes of commercially available OraPlus/OraSweet. Each suspension containing amlodipine 1 mg/mL was stored in 10 plastic prescription bottles; 5 were stored at 4°C and 5 at 25°C. Samples were collected immediately after preparation (day 0) and on days 7, 14, 28, 42, 56, 70, and 91. Amlodipine concentration was measured by stability-indicating HPLC method (n = 15). ***Setting:*** Research laboratory at Children's Hospital. ***Main Outcome Measures:*** Physical and chemical stability (> 90% of the initial concentration) of amlodipine in the two extemporaneously prepared suspensions during storage in plastic prescription bottles at 4°C and 25°C. ***Results:*** Observed mean concentrations exceeded 90% of the initial concentrations in both suspensions for 91 days at 4°C and 56 days at 25°C. No noticeable change in physical appearance or odor was observed; pH changed slightly in the methylcellulose-containing formulation stored at 25°C. ***Conclusion:*** Amlodipine was stable in two suspensions when stored in plastic prescription bottles for 91 days at 4°C or 56 days at 25°C. These formulations may be considered for pediatric or elderly patients who are unable to swallow tablets. The liquid dosage form would also permit accurate administration of amlodipine doses to infants and young children based on their body weight.

J Am Pharm Assoc. 1999;39:375–7.

Calcium antagonists are used in pediatric patients with hypertension. Nifedipine is the most commonly used drug; however, it has a short duration of action and there is no liquid dosage form for children. Amlodipine besylate, another dihydropyridine calcium antagonist, has a longer elimination half-life, allowing once-daily dosing.[1–4] Because oral amlodipine is available only in tablet form, we designed a study to determine its stability in two extemporaneously prepared suspensions stored under refrigeration and at room temperature.

Calcium antagonists are among the majority of the drugs approved only for adults, and yet are routinely used in infants and children. These drugs include albuterol, captopril, digoxin, morphine, and ranitidine. A drug not labeled for pediatric use is often commercially unavailable in a suitable oral liquid dosage form.

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Methods

Amlodipine besylate (Norvasc—Pfizer; 50 tablets, 5 mg each)[a] tablets were ground to powder using a mortar and pestle, then two 250 mL suspensions were prepared: the first in 1:1 simple syrup NF[b] with 1% methylcellulose[a,c] (see Appendix), while mixing; the second in 1:1 OraSweet[d]: OraPlus,[a] while mixing. Concentration of amlodipine in each suspension was 1 mg/mL.

Both suspensions were stored in 10 amber plastic[f] prescription bottles (2 oz. each). Five bottles of each suspension were stored at 4°C in a refrigerator,[g] and another set of five bottles were stored at 25°C in a temperature-controlled water bath.[h] Each bottle was removed from its 5-minute medium agitation setting (6 on a scale of 1 to 10 at a 30° angle) on the wrist action shaker, and gently inverted three times by hand to avoid trapping unwanted air bubbles. The inversion procedure was repeated between each of the aliquots. Immediately after shaking, three 500 µL samples were drawn from the approximate center of the

Table 1. Stability of Amlodipine in Two Suspensions at 4°C and 25°C

	% Mean (± SD) Initial Concentration Remaining (n = 15)			
	25°C		4°C	
Day	1% MC/Syrup[a]	OS/OP[b]	1% MC/Syrup[a]	OS/OP[b]
0	100% ± 1.28[c] (pH 6.69 ± 0.005)	100% ± 2.14[d] (pH 4.58 ± 0.008)	100% ± 0.97[e] (pH 6.68 ± 0.005)	100% ± 1.98[f] (pH 4.58 ± 0.008)
7	99.21 ± 1.83	100.27 ± 2.16	100.21 ± 1.13	99.99 ± 2.04
14	98.72 ± 1.67	99.06 ± 1.99	99.63 ± 1.01	99.53 ± 1.71
28	97.27 ± 1.52	98.13 ± 2.27	99.17 ± 1.11	99.19 ± 2.18
42	94.76 ± 1.28	96.62 ± 2.84	98.47 ± 1.23	98.84 ± 2.36
56	92.39 ± 2.01	95.47 ± 3.09	97.21 ± 1.44	97.86 ± 2.73
70	89.67 ± 1.89	93.11 ± 3.25	96.92 ± 1.88	97.03 ± 3.04
91	87.63 ± 2.75 (pH 6.50 ± 0.016)	90.72 ± 3.83 (pH 4.61 ± 0.007)	94.27 ± 2.49 (pH 6.69 ± 0.007)	95.87 ± 3.42 (pH 4.59 ± 0.008)

MC = methylcellulose; OP = OraPlus; OS = OraSweet.
[a] 1% methylcellulose in syrup.
[b] 1:1 mixture of OraPlus and OraSweet.
Actual initial concentrations (mean ± SD) were
[c] 1.06 ± 0.01 mg/mL
[d] 0.99 ± 0.02 mg/mL
[e] 1.02 ± 0.04 mg/mL
[f] 1.03 ± 0.08 mg/mL

liquid volume in each bottle on days 0, 7, 14, 28, 42, 56, 70, and 91. A high-performance liquid chromatography (HPLC) method[6] was modified to measure amlodipine concentration in each sample in duplicate. The pH was also measured in each sample using a digital pH meter.

The HPLC instrumentation included Hewlett-Packard (HP) 1050 pump,[i] HP 1050 autosampler,[j] HP 1050 variable wavelength detector,[k] and HP 3396A integrator.[l] Other equipment included a Zorbax CN 3.0 × 150 mm,[m] digital pH meter,[n] Burrell Wrist Action Shaker,[o] and Vortex Genie 2.[p]

The chemicals and reagents were American Chemical Society or analytical grade. These included acetonitrile,[q] methanol,[r] buffer solution pH 7.00,[s] buffer solution pH 4.00,[t] and buffer solution pH 10.00.[u] The mobile phase consisted of 35% 40 mM ammonium acetate[v] and 15% methanol and 50% acetonitrile filtered through a 0.45 mμ nylon 66 filter[w] then degassed with helium.

Stock solution of amlodipine[x] was prepared in methanol then diluted to yield concentrations of 1.50, 1.25, 1.00, 0.75, 0.50, 0.25, and 0.10 mg/mL. Of these, 100 μL of each sample was mixed with 5.0 mL of internal standard solution (desipramine HCl[y] 20.0 μg/mL in mobile phase), centrifuged, and the supernatant was analyzed in the same manner as the samples. Flow rate was 0.4 mL/minute, the detector was set at 240 nm, and injection volume was 10 μL. The column was maintained at ambient temperature.

To establish the stability-indicating nature of the method, amlodipine 1.0 mg/mL was subjected to a forced acid (2.0 M HCl),[z] base (2.0 M NaOH)[aa] hydrolysis and oxidation (0.03% H_2O_2)[bb] at 60°C. The sample was analyzed as described earlier every 30 minutes until about one-half of the amlodipine peak disappeared, to show that the quantification of amlodipine was not influenced by degradation products. Each chromatographic run required about 10 minutes. Amlodipine and desipramine eluted at approximately 6.4 and 8.8 minutes, respectively. Linearity was determined by linear regression analysis of amlodipine concentration based on peak area ratios of amlodipine to internal standard. The correlation coefficient was greater than 0.999 with a coefficient of variation less than 1.9% intraday and 2.6% interday.

Results and Discussion

In each extemporaneously prepared suspension, amlodipine besylate was stable for 91 days at 4°C and 56 days at 25°C (Table 1). No noticeable changes in color or odor were observed in any sample during the 91-day study period; the pH changed slightly in 1% methylcellulose/syrup formulation at 25°C. These data should be useful for preparing a liquid dosage form of amlodipine for pediatric patients who are unable to swallow tablets. In addition, it would be possible to accurately measure doses/kilogram of body weight, as is routinely done in pediatric practice.

When a liquid dosage form is not available commercially, tablets may be crushed to prepare powder papers for individual doses. However, this practice is extremely cumbersome and time consuming. In addition, mixing by caregivers in various vehicles may lead to errors in drug administration.

The stability data in two suspensions offer an opportunity to either use commercially available suspending agent and syrup or to prepare the suspending agent extemporaneously. The latter alternative may be less expensive, but many pharmacists

may not have access to methylcellulose or an interest in preparing it. Both suspensions were sweet and acceptable in taste. The formulation in 1% methylcellulose/syrup settled slightly faster than the Ora Plus/Ora Sweet formulation, but both resuspended easily after shaking.

Based on our data, it would be feasible to provide a liquid formulation of amlodipine in plastic prescription bottles to be stored under refrigeration. Although the drug was stable at room temperature for 8 weeks, we cannot rule out the possibility of microbial contamination during extended storage. The auxiliary label should indicate "Shake Well" and "Refrigerate"; the expiration date at 4°C should be less than 3 months. By showing that frequent prescription refills are not required for amlodipine besylate, our data should improve convenience for the patient and/or caregiver.

Conclusion

Amlodipine besylate was stable in two extemporaneously prepared suspensions stored in plastic prescription bottles for 3 months under refrigeration and 8 weeks at room temperature. These formulations may be considered for pediatric or elderly patients who are unable to swallow tablets. The liquid dosage form would also permit accurate administration of amlodipine doses to infants and young children based on their body weight.

Appendix

Preparation of 1% Methylcellulose (1 Liter)[s]

Purified water (200 mL) was heated to boiling. Methylparaben (200 mg) and propylparaben (100 mg) were added and mixed well. Methylcellulose provider (10 g; 4,000 cps) was added, allowed to stand for 15 minutes, then removed from heat. The cold purified water was added to make a total volume of 1 liter, while mixing well with magnetic stirrer. The mixing was continued to make a clear, homogenous preparation.

[a]Lot 6QP114A, Pfizer Inc., Groton, Conn.
[b]Lot 33874, Humco Laboratory, Texarkana, Tex.
[c]Lot CH109608MG, Children's Hospital, Columbus, Ohio. OraPlus (microcrystalline cellulose, carboxymethylcellulose, xanthan gum, carrageenan, preservative, and other excipients).
[d]Lot 5K6734, Paddock Laboratories, Minneapolis, Minn. OraSweet (sucrose, glycerin, sorbitol, preservative, and other excipients).
[e]Lot 4E6462, Paddock Laboratories, Minneapolis, Minn.
[f]Ol Owens-Illinois, Toledo, Ohio.
[g]White-Westinghouse, White Consolidated Inc., Columbus, Ohio.
[h]Lauda RM20, Brinkman Instruments, Inc., Westbury, N.Y.
[i]Hewlett-Packard Co., Analytical Products Group, Palo Alto, Calif.
[j]Hewlett-Packard Co., Analytical Products Group, Palo Alto, Calif.
[k]Hewlett-Packard Co., Analytical Products Group, Palo Alto, Calif.
[l]Hewlett-Packard Co., Analytical Products Group, Palo Alto, Calif.
[m]MAC-MOD Analytical, Inc. Chadds Ford, Pa.
[n]Orion, model 701A, Orion Research Inc., Boston Mass.
[o]Burrell Corp., Pittsburg, Pa.
[p]Fisher Scientific, Pittsburgh, Pa.
[q]Lot BM572, Burdick & Jackson, Div. of Baxter, Muskegon, Mich.
[r]Lot BN751, Burdick & Jackson, Div. of Baxter, Muskegon, Mich.
[s]Fisher lot 91090-24, Fisher Scientific, Pittsburgh, Pa.
[t]Fisher lot 910043-23, Fisher Scientific, Pittsburgh, Pa.
[u]Fisher lot 908624-24, Fisher Scientific, Pittsburgh, Pa.
[v]Lot 06813TX, Aldrich Chemical Co., Milwaukee, Wisc.
[w]Lot 0082205, Gelman Sciences, Ann Arbor, Mich.
[x]Lot 5C077-05CCS-10, Pfizer Inc., Groton, Conn.
[y]Lot 84H088, Sigma Chemical Co., St. Louis, Mo.
[z]Lydrochloric acid lot AB12K8SV, Mallinckrodt Specialty Chemical Co., Chesterfield, Mo.
[aa]Sodium hydroxide lot 0011ODY, Aldrich Chemical Co., Milwaukee, Wisc.
[bb]Hydrogen peroxide lot 05427TX, Aldrich Chemical Co., Milwaukee, Wisc.

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